

Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake

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Dietary restriction has been shown to have several health benefits including increased insulin sensitivity, stress resistance, reduced morbidity, and increased life span. The mechanism remains unknown, but the need for a long-term reduction in caloric intake to achieve these benefits has been assumed. We report that when C57BL/6 mice are maintained on an intermittent fasting (alternate-day fasting) dietary restriction regimen their overall food intake is not decreased and their body weight is maintained. Nevertheless, intermittent fasting resulted in beneficial effects that met or exceeded those of caloric restriction including reduced serum glucose and insulin levels and increased resistance of neurons in the brain to excitotoxic stress. Intermittent fasting therefore has beneficial effects on glucose regulation and neuronal resistance to injury in these mice that are independent of caloric intake.

caloric restriction | hippocampus | insulin | β -hydroxybutyrate | ketosis

Aging refers to the biological changes that occur during a lifetime that result in reduced resistance to stress, increased vulnerability to disease, and an increased probability of death. The rate at which aging occurs is species-specific, suggesting a strong genetic influence. The only environmental variable that has been shown to markedly affect the rate of aging in a wide range of species is caloric intake. Restricting food intake to a level below that which would be consumed voluntarily results in a decrease in the rate of aging and an increase in average and maximum life span (1, 2). Dietary restriction (DR) reduces cancer formation (3, 4) and kidney disease (5) and increases the resistance of neurons to dysfunction and degeneration in experimental models of Alzheimer's and Parkinson's diseases as well as stroke (6–9). Two different DR paradigms have proven effective in increasing life span and disease resistance in rats and mice. In one paradigm animals are provided a daily food allotment that is typically 30–40% less than the *ad libitum* (A.L.) consumption of a control population; this limited daily feeding (LDF) paradigm involves a controlled caloric restriction and a corresponding reduction in body weight. In the second paradigm animals are subjected to intermittent (alternate-day) fasting (IF), which in rats results in reduced food intake over time and decreased body weight (10).

Restricting caloric intake causes the restricted population to weigh proportionally less than the A.L.-fed group. Indeed, weight reduction typically slightly exceeds the degree of food restriction, so that food intake per gram of body weight is reported consistently to be slightly higher in LDF animals than in their A.L.-fed counterparts (11). Rats and mice usually lose weight when maintained on an IF regimen, although some strains such as C57BL/6 mice may lose little or no weight (12). Both the IF and LDF paradigms are reported to result in dramatic increases in life span in comparison to A.L.-fed animals (13), but little else is known concerning the similarities and differences in their effects.

It seems reasonable to assume that both LDF and IF paradigms of DR extend life span through a common mechanism. To gain insight into the nature of the underlying mechanism, we compared the effects of LDF and IF diets on several parameters that have been postulated to play a role in the protective effects of DR including body weight, food intake, and fasting levels of serum insulin, glucose, and insulin-like growth factor 1 (IGF-1). In addition, recent studies have shown that rats and mice maintained on an IF regimen exhibit increased resistance of neurons in their brains to insults relevant to the pathogenesis of several different human neurological disorders including epileptic seizures and stroke (6, 8, 14). We therefore performed an experiment to determine whether LDF and IF diets exert similar beneficial effects on neurons in the brain.

Materials and Methods

Animals and Measurements of Body Weight and Food Intake. Six-week-old C57BL/6 mice were obtained from Charles River Breeding Laboratories, housed in the National Institute on Aging Gerontology Research Center animal colony, and fed a standard NIH-07 diet (Harlan-Teklad, Indianapolis). Food was provided A.L. until 9 weeks of age. At that time, mice were assigned to one of three groups: A.L., fed *ad libitum*; IF, provided access to food every other day; and LDF, provided with a limited daily food allotment of 60% of that eaten by the A.L.-fed animals. To control for caloric intake versus periodic food deprivation, a fourth group was added: These pair-fed (PF) mice were provided daily with a food allotment equal to the average daily intake of mice in the IF group. Water was available A.L. for all groups. The animals were kept in a 12-h light/12-h dark cycle (lights on at 6 a.m. and off at 6 p.m.); food was provided or removed at 10 a.m. Body weight was determined each week on the same day and time. Food intake was measured daily. To keep track of spillage, white bedding was used to allow easy separation of unconsumed food and powder from waste and bedding; spilled food was allowed to dry fully to avoid measurement of wet weight added by urine. Statistical comparisons were made by using ANOVA. All procedures were approved by the National Institute on Aging Gerontology Research Center Animal Care and Use Committee.

Blood Collection and Analyses. At 29 weeks of age, all mice were fasted for 14 h before blood withdrawal. Blood was removed via intracardiac bleed under isoflurane anesthesia, and serum was

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Kumar, Sanjay Agarwal, 2021-03-31 Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced The latest edition of this reference provides endocrinologists with the latest advances in the diagnosis and management of diabetes Beginning with an overview of epidemiology pathophysiology and metabolism the next sections discuss presentations of diabetes therapeutic management complications and comorbidities The following chapters cover diabetes in certain population groups education and technology nutrition glucose monitoring and research The book concludes with a section dedicated to Type 1 diabetes and a selection of journal reviews Flow diagrams tables and figures further enhance the comprehensive text Key points Latest edition of comprehensive reference detailing latest advances in diagnosis and management of diabetes Covers numerous therapeutic methods Complete sections dedicated to Type 1 diabetes and journal reviews Highly illustrated with flow diagrams tables and figures **Advances in Central Nervous System Research and Treatment: 2012 Edition** ,2012-12-26

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